

High-Normal Thyroid-Stimulating Hormone Shows a Potential Causal Association With Arrhythmia Recurrence After Catheter Ablation of Atrial Fibrillation

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Background—Hypothyroidism has been shown to contribute to enhanced atrial arrhythmogenesis, resulting in atrial fibrillation (AF) development in animal models and clinical populations. We aimed to elucidate whether high thyroid-stimulating hormone (TSH) levels are related to outcomes of catheter ablation of AF.

Methods and Results—Of 477 consecutive patients who underwent first-time pulmonary vein isolation–based radiofrequency catheter ablation of AF, 456 with TSH above the lower limit of the normal range (age, 65.5 ± 9.9 years; men, 73.9%; paroxysmal AF, 56.8%) were analyzed for this study. Atrial tachyarrhythmia recurrence for 3 years was compared across groups with hypothyroidism ($n=23$) and TSH quartile groups with euthyroidism (normal-range TSH levels, $n=433$). Atrial tachyarrhythmia recurrence occurred in 179 patients (39%) after the first session. Patients with hypothyroidism had increased recurrence compared with patients with normal TSH levels (crude hazard ratio, 3.14 after the last session; $P=0.001$). When focusing on patients with normal TSH levels, recurrence-free survivals after both the first and last sessions were significantly reduced in euthyroid patients with the highest quartile of TSH levels (quartile 4) compared with others (quartiles 1–3). Cox regression analysis identified high TSH levels as an independent predictor of atrial tachyarrhythmia recurrence after both the first (adjusted hazard ratio, 1.51; $P=0.018$) and last (adjusted hazard ratio, 1.86; $P=0.023$) sessions. The difference was more pronounced in patients with paroxysmal AF than in those with nonparoxysmal AF.

Conclusions—Not only hypothyroidism but also high-normal TSH levels may be an independent predictor of atrial tachyarrhythmia recurrence after catheter ablation of AF. (*J Am Heart Assoc.* 2018;7:e009158. DOI: 10.1161/JAHA.118.009158.)

Key Words: atrial fibrillation • catheter ablation • hypothyroidism • recurrence • thyroid-stimulating hormone

It is well known that thyroid hormonal abnormalities, both hyperthyroidism and hypothyroidism, are intimately associated with cardiovascular disorders. Thyroid hormone has ubiquitous effects on the major components of the circulatory system, such as the heart and the blood vessels, and modulates every component of the cardiovascular organs. Therefore, when cardiovascular disease is present, clinicians usually determine whether thyroid disorders are concomitantly

present in individuals. In particular, hyperthyroidism, either overt or subclinical, is known to carry a risk of atrial fibrillation (AF), often inducing heart failure.^{1–3}

The role of hypothyroidism in atrial arrhythmogenesis, however, is less recognized and is not fully understood.² Subclinical hypothyroidism was defined as a state with elevated serum thyroid-stimulating hormone (TSH) levels with thyroid hormone levels within the reference range, and the thyroid dysfunction is compensated for by the greater stimulation of the elevated TSH level and also increases the risk of cardiovascular events.⁴ Clinically, a close association of hypothyroidism history with the occurrence of AF was suggested in patients enrolled for >10 years.⁵ In an animal study, it was demonstrated that hypothyroidism leads to an increase in AF vulnerability.⁶

Catheter ablation for AF, a common treatment to prevent recurrent AF or convert persistent AF to sinus rhythm, is primarily achieved through isolation of the pulmonary veins (PVs), which generally function as sources of AF by triggering premature contractions. Given the demonstrated association of AF occurrence with hypothyroidism, hypothyroidism may also unfavorably affect the outcome of catheter ablation for

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Clinical Perspective

What Is New?

- Not only hypothyroid patients but also those with a high-normal thyroid-stimulating hormone level are at higher risk of long-term atrial tachyarrhythmia recurrence after pulmonary vein isolation–based catheter ablation for atrial fibrillation (AF), especially for paroxysmal AF.

What Are the Clinical Implications?

- There have been studies highlighting the heterogeneity of cases of paroxysmal AF, focusing on the subgroup of paroxysmal AF that shares the same arrhythmia substrate as nonparoxysmal AF and is resistant to pulmonary vein isolation as a result.
- Our findings provide new insight into this mechanistic overlap theory between patients with paroxysmal and nonparoxysmal AF.
- There may be additional strategies using medication and ablation procedures for long-term success of treatment of AF in patients with high thyroid-stimulating hormone levels.

AF. In this regard, however, few data have been available. This study was designed to elucidate the association of overt and subclinical hypothyroidism and high-normal TSH levels with atrial tachyarrhythmia recurrence after PV isolation (PVI)–based radiofrequency catheter ablation for AF.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because the original data included the patients' personal information.

Study Population

From January 1, 2011, through June 30, 2015, 477 consecutive patients who underwent first-time radiofrequency catheter ablation for paroxysmal AF or persistent AF, including long-standing AF (nonparoxysmal AF), were enrolled at our institute. We evaluated thyroid hormone function by measuring the levels of TSH, free triiodothyronine, and free thyroxine. First, patients with TSH levels below the reference range (hyperthyroidism) were excluded from analysis. Second, patients diagnosed clinically with overt and subclinical hypothyroidism were compared with the remaining patients having TSH levels within the reference range, indicating normal thyroid function ("euthyroidism"). Third, patients with euthyroidism were divided into quartiles according to TSH levels, regardless of free triiodothyronine or thyroxine levels,

history of hyperthyroidism or hypothyroidism, or medications for hyperthyroidism, hypothyroidism, and arrhythmia, and were analyzed. The levels of TSH, free triiodothyronine, and free thyroxine were also determined using an electrochemiluminescence immunoassay within a week before the ablation. The reference ranges for TSH, free triiodothyronine, and free thyroxine were 0.4 to 4.2 mIU/mL, 2.3 to 4.1 pg/mL, and 0.88 to 1.50 ng/dL, respectively.

We evaluated the risk scores for predicting ischemic stroke in clinical practice by using the CHADS₂ score (scored as 1 point each for congestive heart failure, hypertension, age ≥ 75 years, and diabetes mellitus, and 2 points for past stroke or transient ischemic attack) on hospital admission. Anticoagulation therapy with warfarin or direct oral anticoagulants was initially introduced for all patients at least 3 weeks before the ablation procedure, as recommended by the expert consensus statement.⁷

Ablation Procedure

After written informed consent was obtained from the patients, ablation procedures were performed under local anesthesia with mild conscious sedation. Extensive encircling PVI, broadly isolating ipsilateral superior and inferior PVs simultaneously, was performed with the use of double circular catheters. An irrigation catheter, in combination with a 3-dimensional mapping system (CARTO [Biosense-Webster, Diamond Bar, CA] or Ensite NavX [St Jude Medical, St Paul, MN]), was used in most patients. Intravenous heparin was administered continuously to maintain an activated clotting time between 300 and 350 seconds. Radiofrequency energy was applied to the antrum of the ipsilateral PVs to create the contiguous lesions. The electrophysiological end point of PVI was a bidirectional conduction block between the left atrium (LA) and PVs. Decisions on whether to perform additional ablations (ie, cavotricuspid isthmus ablation, superior vena cava isolation, continuous fractionated atrial electrogram ablation, ganglionated plexi ablation, or LA linear ablation) were left to the discretion of the operator.

Follow-Up

Patients received periodic follow-up at the outpatient clinic at 1, 3, 6, 12, 24, and 36 months after the initial and the subsequent repeated ablation procedures, if performed. When patients had symptoms, 1-channel ECGs were recorded with the use of an ambulatory electrogram recorder (HCG-801; Omron Healthcare, Kyoto, Japan) to correlate with the symptoms. Repeated ablation during the blanking period of 90 days after ablation was strongly discouraged. Discontinuation of antiarrhythmic drugs was encouraged at 3 months after the procedure. A 12-lead ECG and 24-hour Holter

monitoring were obtained at every visit. The follow-up was ended in June 2016, by which time all the patients had completed a minimum follow-up period of 12 months since the initial ablation procedure. The missing follow-up data were obtained by contacting the physicians in charge or the patients themselves.

Study Outcome

The primary end point of the study was defined as the recurrence of atrial tachyarrhythmia during the 3 years, with a blanking period of 90 days after the first AF ablation. The secondary end point of the study was recurrence of atrial tachyarrhythmia, with a blanking period of 90 days after the last session. The definitions of recurrent atrial tachyarrhythmias were those lasting for >30 seconds or requiring repeated ablation. When repeated ablation was performed within 90 days after ablation, the patient was considered as having recurrent arrhythmia at day 91. The study complied with the Declaration of Helsinki. The study protocol was approved by the institutional review board at Ogaki Municipal Hospital (Ogaki, Japan).

Statistical Analysis

Continuous baseline and outcome variables are expressed as means \pm SDs for normally distributed data and medians and interquartile ranges for nonnormally distributed data, whereas discrete variables are given as absolute values, percentages, or both. Continuous variables were compared using Student *t* test for divided patients into 2 groups and 1-way ANOVA among 4 groups. For nonnormally distributed data and ordinal variables, the Mann-Whitney *U* test and Kruskal-Wallis *H* test were used in comparisons of 2 and 4 groups, respectively. To compare the rates of categorical variables, the χ^2 test was used. Long-term survival was analyzed using the Kaplan-Meier method and log-rank (Mantel-Cox) test. The Cox proportional hazards model was also used for univariate and multivariable analysis of survival. Variables included in the multivariate analysis consist of selected variables based on the association with atrial tachyarrhythmia recurrence ($P<0.10$) and other general variables. They were paroxysmal AF, amiodarone prescription, LA dimension (LAD) >40 mm, left ventricular ejection fraction $\geq 60\%$, age ≥ 75 years old, and sex, in addition to hypothyroidism for the analysis including all patients or the highest quartile of TSH levels for the analysis among patients with euthyroidism. Statistical analyses were performed in R, version 3.4.2 (<https://cran.r-project.org>). $P<0.05$ was considered statistically significant.

Results

Of the 477 patients, 21 with TSH levels below the reference range were excluded from analysis because of suspected

hyperthyroidism. Among the 23 patients with TSH levels above the normal range, 11 showed free thyroxine levels lower than the reference range (overt hypothyroidism) and 12 showed normal free thyroxine levels (so-called subclinical hypothyroidism). Both were combined into one group as hypothyroidism group for analysis. Among patients whose TSH levels were within the normal range (so-called euthyroidism), we compared data of the high-normal TSH group (the highest quartile of TSH levels, quartile 4) with those of the remaining patients (quartile 1–3) in addition to comparisons among the 4 quartiles.

Hypothyroidism Versus Euthyroidism

Baseline characteristics of the patients are shown in Table 1. The mean TSH levels in the hypothyroidism group ($n=23$) were ≈ 6 -fold higher than those in the normal TSH group ($n=433$) (9.80 ± 10.44 versus 1.56 ± 0.79 $\mu\text{IU/mL}$; $P<0.001$). The mean free triiodothyronine and free thyroxine levels in the hypothyroidism group were significantly lower than those in the normal TSH group. The patients with hypothyroidism had larger LAD (43.1 ± 6.9 versus 39.0 ± 6.8 mm; $P=0.006$), included less paroxysmal AF (34.8% versus 58.0%; $P=0.032$), and were more frequently taking class 3 antiarrhythmic drugs, including amiodarone (26.1% versus 5.8%; $P=0.003$), than those with the normal TSH group. In terms of catheter ablation procedures, all patients underwent PVI. Cavotricuspid isthmus ablation was added to most patients. However, additional substrate-modifying procedures, such as ablation of continuous fractionated atrial electrogram, LA lines, ganglionated plexi ablation, and superior vena cava isolation, were only performed in limited numbers of patients. No significant differences in add-on ablation procedures were observed among the patient groups, as shown in Table 2.

Two patients (0.4%) were unavailable for follow-up before June 2016; however, their follow-up periods were >3 years and 33 months, respectively. With regard to clinical prognosis up to 3 years, atrial tachyarrhythmia recurred in 179 of 456 patients (39%) after the first session. Of them, 12 patients (2.6%) underwent repeated ablation within the 90-day blanking period after the initial session because of uncontrollable symptoms of atrial tachyarrhythmia. The atrial tachyarrhythmia-free survival was marginally lower in the hypothyroidism group than in the normal TSH group, but the difference did not reach statistical significance (crude hazard ratio [HR], 1.66; 95% confidence interval [CI], 0.95–2.93; $P=0.077$ by Cox hazard analysis) (Figure 1A). The hypothyroidism group showed significantly lower atrial tachyarrhythmia-free survival than the normal TSH group after the last session, with an average of 1.4 ± 0.6 ablation procedures (crude HR, 3.14; 95% CI, 1.56–6.31; $P=0.001$ by Cox hazard analysis) (Figure 1B). Multivariate analysis identified hypothyroidism (adjusted HR,

Table 1. Baseline Characteristics of the Subjects Assigned by TSH Levels

Characteristics	All Patients (N=456)	Normal TSH (n=433)	Hypothyroidism (n=23)	P Value	Normal TSH by Quartile				P Value Among Quartile 1 to Quartile 4	P Value Between Quartile 1-3 vs Quartile 4	
					1 (n=109)	2 (n=108)	3 (n=109)	4 (n=107)			
Thyroid function											
TSH, μ IU/mL	1.98 \pm 3.02	1.56 \pm 0.79	9.80 \pm 10.44	<0.001	0.71 \pm 0.16	1.17 \pm 0.12	1.70 \pm 0.18	1.19 \pm 0.43	2.69 \pm 0.54	<0.001	<0.001
Free triiodothyronine, pg/mL	3.35 \pm 0.37	3.36 \pm 0.37	3.09 \pm 0.31	<0.001	3.50 \pm 0.34	3.42 \pm 0.31	3.32 \pm 0.33	3.41 \pm 0.33	3.22 \pm 0.43	<0.001	<0.001
Free thyroxine, ng/dL	1.09 \pm 0.22	1.10 \pm 0.21	0.87 \pm 0.24	<0.001	1.16 \pm 0.19	1.09 \pm 0.20	1.08 \pm 0.20	1.11 \pm 0.20	1.07 \pm 0.23	0.010	0.079
Age, y	65.5 \pm 9.9	65.4 \pm 10.1	67.8 \pm 7.1	0.26	62.3 \pm 11.3	64.5 \pm 10.2	66.1 \pm 9.3	64.3 \pm 10.4	68.8 \pm 8.1	<0.001	<0.001
Male sex	337 (73.9)	317 (73.2)	20 (87.0)	0.22	88 (80.7)	82 (75.9)	83 (76.1)	253 (77.6)	64 (59.8)	0.003	0.001
BMI, kg/m ²	23.7 \pm 3.4	23.7 \pm 3.4	24.8 \pm 3.1	0.11	23.5 \pm 3.1	23.7 \pm 3.5	24.1 \pm 3.5	23.8 \pm 3.4	23.3 \pm 3.5	0.32	0.17
CHADS2 score, mean	1.21 \pm 1.07	1.19 \pm 1.06	1.57 \pm 1.08	0.10	1.10 \pm 1.09	1.15 \pm 1.04	1.35 \pm 1.08	1.20 \pm 1.07	1.17 \pm 1.04	0.34	0.79
0 or 1	310 (68.0)	299 (69.1)	11 (47.8)	0.078	77 (70.6)	76 (70.4)	70 (64.2)	223 (68.4)	76 (71.0)	0.58	0.48
2	93 (20.4)	85 (19.6)	8 (34.8)		21 (19.3)	24 (22.2)	23 (21.1)	68 (20.9)	17 (15.9)		
≥ 3	53 (11.6)	49 (11.3)	4 (17.4)		11 (10.1)	8 (7.4)	16 (14.7)	35 (10.7)	14 (13.1)		
Hypertension	241 (52.9)	226 (52.2)	15 (65.2)	0.29	57 (52.3)	53 (49.1)	66 (60.6)	176 (54.0)	50 (46.7)	0.19	0.22
Diabetes mellitus	77 (16.9)	70 (16.2)	7 (30.4)	0.087	17 (15.6)	23 (21.3)	18 (16.5)	58 (17.8)	12 (11.2)	0.25	0.13
History of heart failure	75 (16.4)	69 (15.9)	6 (26.1)	0.24	18 (16.5)	14 (13.0)	18 (16.5)	50 (15.3)	19 (17.8)	0.79	0.55
Systemic embolism or TIA	41 (9.0)	39 (9.0)	2 (8.7)	>0.99	7 (6.4)	9 (8.3)	12 (11.0)	28 (8.6)	11 (10.3)	0.64	0.57
LVEF, %	65.4 \pm 9.1	65.5 \pm 9.1	63.2 \pm 7.8	0.24	65.5 \pm 8.5	65.4 \pm 10.0	65.7 \pm 9.3	65.5 \pm 9.3	65.6 \pm 8.8	0.99	0.96
LAD, mm	39.3 \pm 6.9	39.0 \pm 6.8	43.1 \pm 6.9	0.006	38.8 \pm 6.8	38.2 \pm 6.1	40.5 \pm 6.7	39.2 \pm 6.6	38.7 \pm 7.4	0.067	0.51
CCR, mL/min	74.3 \pm 26.8	74.9 \pm 27.0	64.5 \pm 21.0	0.072	81.8 \pm 26.2	77.2 \pm 26.3	74.9 \pm 29.3	78.0 \pm 27.4	65.3 \pm 23.3	<0.001	<0.001
BNP, pg/mL	86.9 (36.0–180)	86.9 (34.2–177)	93.5 (63.5–259)	0.15	86.1 (37.6–200)	73.8 (23.1–137)	87.1 (34.1–185)	82.6 (33.2–173)	103.2 (40.6–192)	0.088	0.11
Paroxysmal AF	259 (56.8)	251 (58.0)	8 (34.8)	0.032	60 (55.0)	64 (59.3)	65 (59.6)	189 (58.0)	62 (57.9)	0.90	>0.99
Medications											
Class 1 AAD	79 (17.3)	79 (18.2)	0 (0.0)	0.002	14 (12.8)	27 (25.0)	19 (17.4)	60 (18.4)	19 (17.8)	0.14	>0.99
Class 3 AAD	31 (6.8)	25 (5.8)	6 (26.1)	0.003	3 (2.8)	3 (2.8)	5 (4.6)	11 (3.4)	14 (13.1)	0.002	0.001
Amiodarone	25 (5.5)	19 (4.4)	6 (26.1)	0.001	1 (0.9)	2 (1.9)	3 (2.8)	6 (1.8)	13 (12.1)	<0.001	<0.001
Thyroxine	4 (0.9)	3 (0.7)	1 (4.3)	0.19	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)	0.027	0.015
Methimazole or propylthiouracil	3 (0.7)	3 (0.7)	0 (0.0)	>0.99	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)	0.027	0.015

Continued

Table 1. Continued

Characteristics	All Patients (N=456)	Normal TSH (n=433)	Hypothyroidism (n=23)	P Value	Normal TSH by Quartile					P Value Among Quartile 1 to Quartile 4	P Value Between Quartile 1–3 vs Quartile 4
					1 (n=109)	2 (n=108)	3 (n=109)	1–3 (n=326)	4 (n=107)		
History of hyperthyroidism	4 (0.9)	4 (0.9)	0 (0.0)	>0.99	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)	3 (2.8)	0.10	0.048
History of hypothyroidism	3 (0.7)	3 (0.7)	0 (0.0)	>0.99	0 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.8)	0.027	0.015
History of thyroidectomy	1 (0.2)	1 (0.2)	0 (0.0)	>0.99	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.3)	0 (0.0)	0.40	>0.99

Quartiles 1, 2, 3, and 4 are quartiles in order of serum TSH levels. Values represent means±SDs, numbers (percentages), or medians (interquartile ranges). AAD indicates antiarrhythmic drug; AF, atrial fibrillation; BMI, body mass index; BNP, B-type natriuretic peptide; CCR, creatinine clearance; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; TSH, thyroid-stimulating hormone.

2.28; 95% CI, 1.07–4.84; $P=0.032$) and amiodarone prescription (adjusted HR, 2.22; 95% CI, 1.14–4.33; $P=0.019$) as the remaining significant predictors of atrial tachyarrhythmia recurrence after the last session when adjusted by the following variables: age, sex, LAD, left ventricular ejection fraction, and paroxysmal AF.

Clinical Significance of Relatively High TSH Levels in Euthyroidism

Baseline characteristics of subgroups according to the quartile range of TSH among those with normal TSH levels are shown in Table 1. The mean TSH level in the quartile 4 group was ≈ 2 -fold higher than that in the quartile 1 to 3 group (2.69 ± 0.54 versus 1.19 ± 0.43 $\mu\text{IU/mL}$; $P<0.001$). Both free triiodothyronine and free thyroxine levels in the quartile 4 group were lower than those in quartile 1 to 3 group, but the difference was significant only for free triiodothyronine levels. The quartile 4 group included older age (68.8 ± 8.1 versus 64.3 ± 10.4 years old; $P<0.001$) and fewer male patients (59.8% versus 77.6%; $P=0.001$) than the quartile 1 to 3 groups. There were no differences in the ratio of paroxysmal AF, CHADS2 score, body mass index, LAD, left ventricular ejection fraction, and B-type natriuretic peptide between the quartile 4 and quartile 1 to 3 groups. Renal dysfunction, as indicated by decreasing creatinine clearance in quartile 4, was slightly advanced and similar to that in the hypothyroidism group. Treatment with amiodarone and class 3 antiarrhythmic drugs was more frequent in quartile 4 than in quartile 1 to 3. The ablation procedures performed were almost identical between quartile 4 and quartile 1 to 3 (Table 2).

Kaplan-Meier analysis and the log-rank test revealed that the atrial tachyarrhythmia-free survival after the first session was significantly different among quartile groups, with quartile 4 showing the lowest survival ($P=0.027$) (Figure 2A). This trend became more prominent in the analysis of event-free survival after the last session ($P=0.017$) (Figure 2B). Event-free survivals were still better in quartile 4 than in the hypothyroidism group (Figures 1 and 2). Accordingly, we regarded quartile 4 as a subgroup with a high risk of atrial tachyarrhythmia recurrence as well as the hypothyroidism group and compared the event-free survivals of quartile 4 with those of the combined quartile 1 to 3 group. The patients in quartile 4 had significantly worse event-free survival than those in quartile 1 to 3, both after the first session (crude HR, 1.58; 95% CI, 1.14–2.19; $P=0.006$ by Cox hazard analysis) (Figure 3A) and after the last session (crude HR, 2.12; 95% CI, 1.28–3.50; $P=0.003$) (Figure 3B). The differences appeared to be more prominent in patients with paroxysmal AF after both the first (crude HR, 1.77; 95% CI, 1.14–2.73; $P=0.010$) (Figure 3C) and last (crude HR, 4.16; 95% CI, 1.86–9.29; $P<0.001$) (Figure 3D) sessions. On the other hand, differences

Table 2. Index Catheter Ablation Procedure Among Groups Assigned by TSH Levels

Variable	All Patients (N=456)	Normal TSH (n=433)	Hypothyroidism (n=23)	P Value	Normal TSH by Quartile					P Value Among Quartile 1 to Quartile 4	P Value Between Quartile 1–3 vs Quartile 4
					1 (n=109)	2 (n=108)	3 (n=109)	1–3 (n=326)	4 (n=107)		
Extensive encircling PVI	456 (100)	433 (100)	23 (100)	>0.99	109 (100)	108 (100)	109 (100)	326 (100)	107 (100)	>0.99	>0.99
CFAE ablation	0 (0.0)	0 (0.0)	0 (0.0)	>0.99	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	>0.99	>0.99
GP ablation	11 (2.4)	9 (2.1)	2 (8.7)	0.10	2 (1.8)	4 (3.7)	0 (0.0)	6 (1.8)	3 (2.8)	0.26	0.70
LA linear ablation	44 (9.6)	43 (9.9)	1 (4.3)	0.71	14 (12.8)	7 (6.5)	9 (8.3)	30 (9.2)	13 (12.1)	0.33	0.36
Tricuspid isthmus line	421 (92.3)	398 (91.9)	23 (100)	>0.99	103 (94.5)	98 (90.7)	99 (90.8)	300 (92.0)	98 (91.6)	0.71	0.84
SVC isolation	43 (9.4)	41 (9.5)	2 (8.7)	>0.99	12 (11.0)	10 (9.3)	10 (9.2)	32 (9.8)	9 (8.4)	0.93	0.85
Non-PV/SVC foci ablation	7 (1.5)	6 (1.4)	4 (4.3)	0.31	0 (0.0)	1 (0.9)	4 (3.7)	5 (1.5)	1 (0.9)	0.11	>0.99

Quartile 1, 2, 3, and 4 are quartiles in order of serum TSH levels in patients with normal TSH levels. Values represent numbers (percentages). LA linear ablations included roof, bottom, mitral, and anterior lines. CFAE indicates continuous fractionated atrial electrogram; GP, ganglionic plexi; LA, left atrium; PV, pulmonary vein; PVI, PV isolation; SVC, superior vena cava; TSH, thyroid-stimulating hormone.

were not statistically significant in patients with nonparoxysmal AF after either the first session (crude HR, 1.38; 95% CI, 0.84–2.27; $P=0.21$) (Figure 3E) or the last session (crude HR, 1.32; 95% CI, 0.67–2.59; $P=0.42$) (Figure 3F). Notably, the event-free survivals in quartile 4 with paroxysmal AF were similar to those in patients with nonparoxysmal AF.

Clinical Predictors of Atrial Tachyarrhythmia Recurrence in Euthyroidism

For predictors of atrial tachyarrhythmia recurrence after the first session, Table 3 shows that a high-normal TSH level (quartile 4) and amiodarone prescription were significant variables. After adjusting HRs in multivariate analysis using variables listed in Table 3, a high-normal TSH level was the only significant factor affecting atrial tachyarrhythmia recurrence (adjusted HR, 1.51; 95% CI, 1.07–2.13; $P=0.018$). With regard to recurrence after the last session, crude HRs in quartile 4, paroxysmal AF, amiodarone, and LAD were significant; and after multivariate adjustment, a high-normal TSH level was an independent predictor (adjusted HR, 1.86; 95% CI, 1.09–3.17; $P=0.023$) for atrial tachyarrhythmia recurrence. Paroxysmal AF was also a significant predictor, in this case against recurrence (adjusted HR, 0.43; 95% CI, 0.25–0.74; $P=0.002$).

Discussion

The present study is, to the best of our knowledge, the first to examine the long-term outcome of catheter ablation of AF on hypothyroidism and TSH levels. The major findings of our study were as follows: (1) the patients diagnosed with overt and subclinical hypothyroidism had a significantly higher prevalence of atrial tachyarrhythmia recurrence than those with normal TSH after ablation procedures; (2) patients with a high-normal TSH level (quartile 4) within the normal TSH range had a significantly higher prevalence of atrial tachyarrhythmia recurrence than the lower-TSH quartiles (quartile 1–3); and (3) this trend was more pronounced in the subgroup of paroxysmal AF than in nonparoxysmal AF. Taken together, these findings indicate that patients with a successful AF catheter ablation procedure could be exposed greater to a risk of AF recurrence if their TSH level was even on the high end of the normal range, even more so if they had subclinical or overt hypothyroidism.

Subclinical Hypothyroidism and AF Prevalence: Cohort Studies

Subclinical hypothyroidism with a TSH level above the normal range, as well as overt hypothyroidism, may represent a novel cardiac risk factor.⁸ With respect to AF, previous studies have

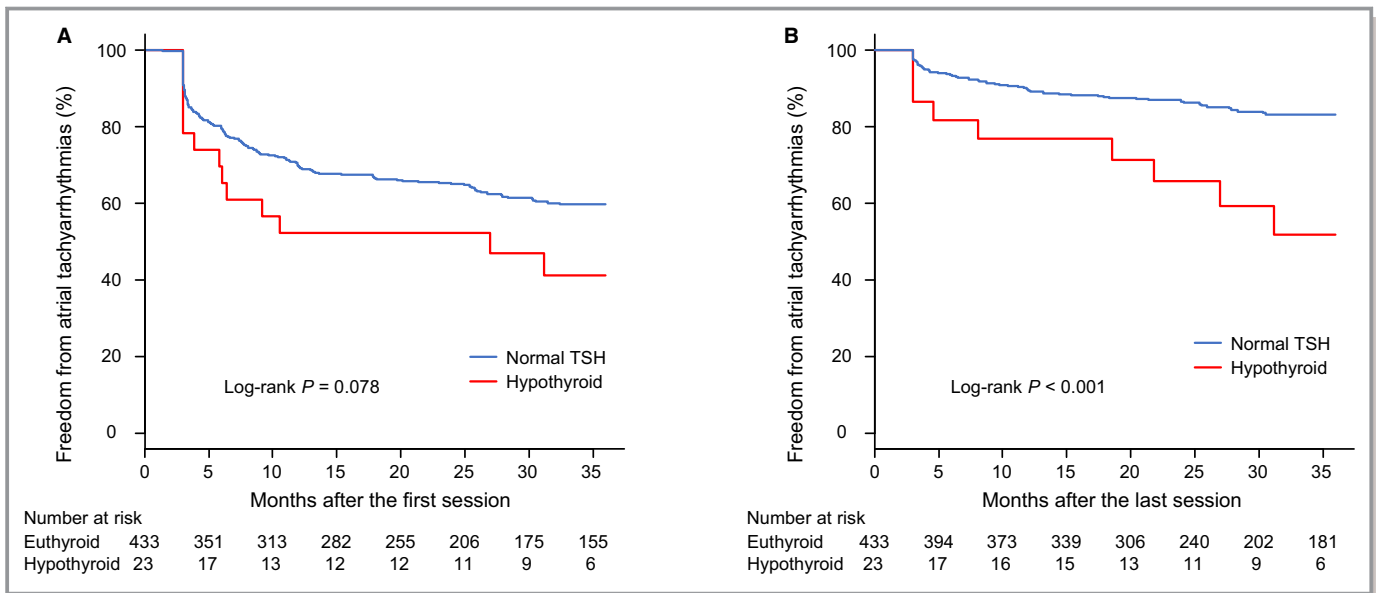


Figure 1. Kaplan-Meier plot of cumulative event-free survival curves in hypothyroid patients undergoing catheter ablation for atrial fibrillation (AF). *P* values calculated by log-rank test. Percentage of no-recurrence patients with normal thyroid-stimulating hormone (TSH) and hypothyroidism in the 3 years after first-time AF ablation for atrial tachyarrhythmia (A) and the last session (B).

failed to show a significant association of subclinical hypothyroidism. There was no significant association between TSH >10 mIU/L and a 10-year risk of incident AF in a community-based study.⁹ A recent systemic review including >30 000 participants showed that, among euthyroid individuals, only a higher circulating free thyroxine level is associated

with increased risk of incident AF.¹⁰ The results do not seem to support our findings. However, the disagreement may be explained by the difference in study population. The large cohort studies targeted patients who had not had AF at the time of inclusion,^{9,10} whereas we studied patients already having AF.

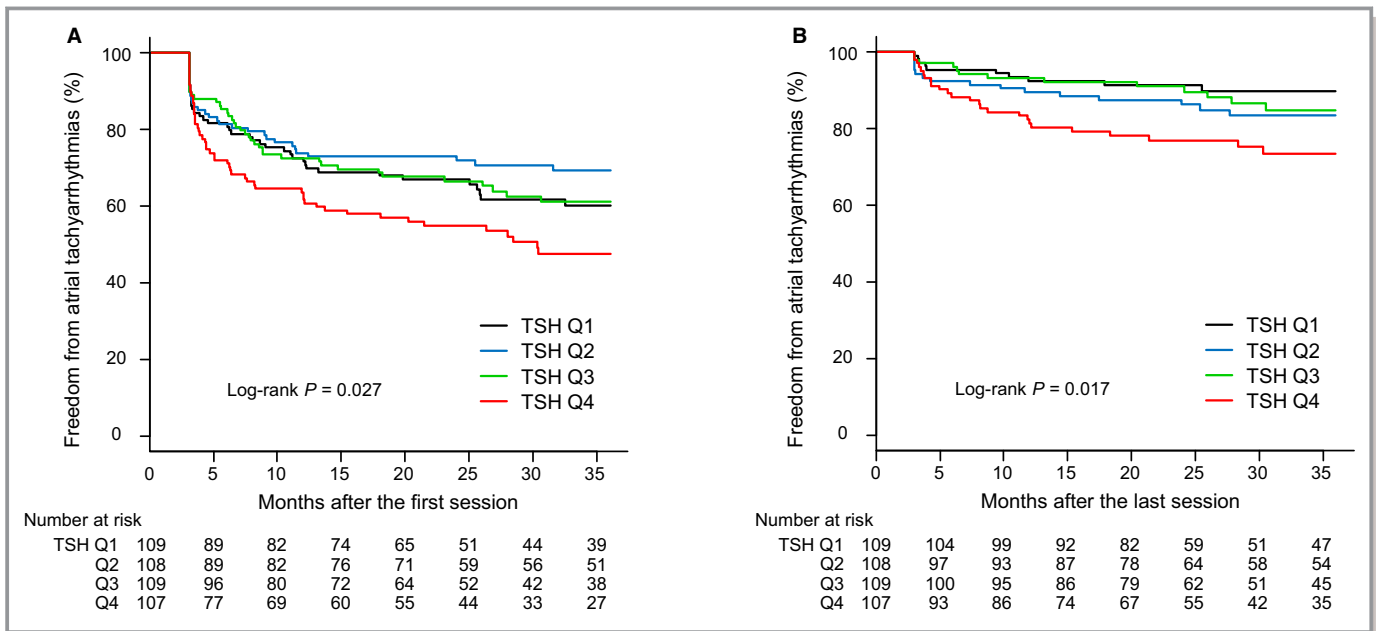


Figure 2. Kaplan-Meier plot of cumulative event-free survival curves in patients with normal thyroid-stimulating hormone (TSH) undergoing catheter ablation for atrial fibrillation (AF). Percentage of 3-year nonrecurrence in patient groups, assigned by TSH levels after first-time AF ablation for atrial tachyarrhythmia (A) and the last session (B). Quartile (Q) 1, Q2, Q3, and Q4 are quartiles in order of TSH levels. *P* values are calculated by log-rank test.

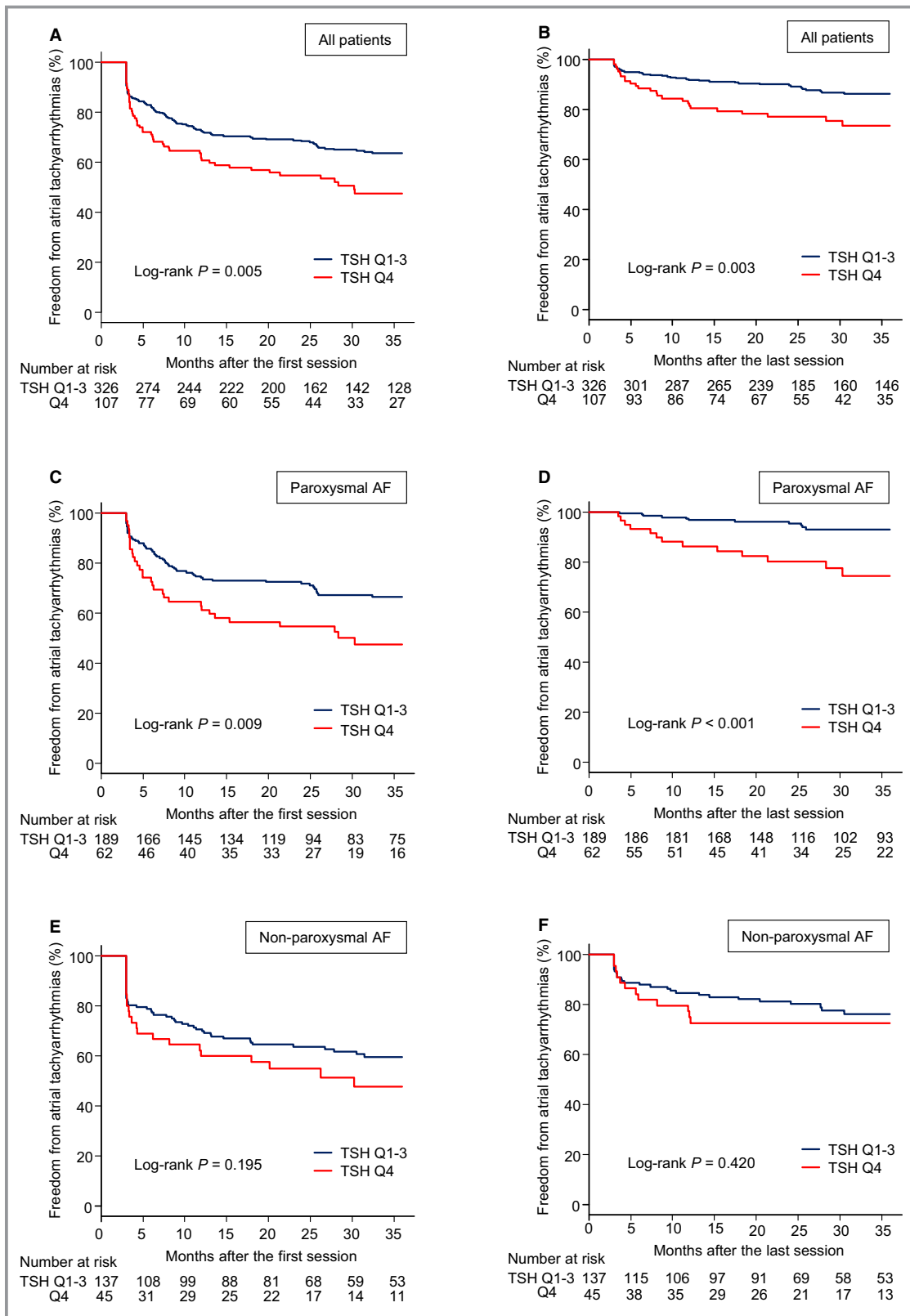


Figure 3. Kaplan-Meier plot of cumulative event-free survival curves in the highest-quartile (quartile [Q] 4) patients with normal thyroid-stimulating hormone (TSH) compared with Q1 to Q3 after undergoing catheter ablation for atrial fibrillation (AF). Percentage of no recurrence in patients with atrial tachyarrhythmia 3 years after the first (A, C, and E) and last (B, D, and F) sessions.

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Table 3. Predictors of Atrial Tachyarrhythmia Recurrence After Catheter Ablation for AF Among Patients With Normal TSH Levels

Variables	Crude HR	95% CI	P Value	Adjusted HR	95% CI	P Value
Atrial tachyarrhythmia recurrence after the first session						
TSH quartile 4	1.58	1.14–2.19	0.006	1.51	1.07–2.13	0.018
Paroxysmal AF	0.81	0.60–1.10	0.18	0.85	0.61–1.17	0.32
Amiodarone prescription	1.83	1.01–3.26	0.045	1.46	0.78–2.72	0.24
LAD >40 mm	1.16	0.85–1.58	0.34	1.06	0.76–1.48	0.73
LVEF ≥60%	0.95	0.64–1.39	0.78	1.03	0.69–1.53	0.89
Age ≥75 y	1.16	0.78–1.74	0.47	1.16	0.78–1.74	0.46
Male sex	0.93	0.66–1.30	0.66	1.02	0.72–1.45	0.92
Atrial tachyarrhythmia recurrence after the last session						
TSH quartile 4	2.12	1.28–3.50	0.003	1.86	1.09–3.17	0.023
Paroxysmal AF	0.38	0.23–0.63	<0.001	0.43	0.25–0.74	0.002
Amiodarone prescription	2.72	1.24–5.98	0.012	1.50	0.64–3.52	0.35
LAD >40 mm	1.70	1.04–2.77	0.034	1.21	0.71–2.05	0.49
LVEF >60%	0.66	0.37–1.19	0.17	0.82	0.45–1.51	0.53
Age ≥75 y	1.13	0.60–2.12	0.89	1.00	0.54–1.86	0.99
Male sex	0.75	0.46–1.21	0.70	0.79	0.46–1.37	0.41

Covariates in the multivariate model (adjusted HR) consist of 7 variables listed above. TSH quartile 4 is the highest-quartile with normal TSH. Cox regression analysis is used to assess the univariate and multivariate HRs for atrial tachyarrhythmia recurrence. AF indicates atrial fibrillation; CI, confidence interval; HR, hazard ratio; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; TSH, thyroid-stimulating hormone.

Role of Subclinical Hypothyroidism in AF Development

In addition, evidence has emerged that subclinical hypothyroidism may be a risk factor for developing AF. Sairaku et al demonstrated that LA a- and v-wave pressure and mean LA pressure were significantly higher in patients with subclinical hypothyroidism (TSH >4.5 mIU/L; mean, 5.99 mIU/L) than in those with euthyroidism.¹¹ Park et al have reported a higher incidence of transient AF in patients with subclinical hypothyroidism, defined as TSH >4.1 mIU/L, after coronary artery bypass graft.¹² These facts strongly indicate that even subclinical hypothyroidism induces deteriorating myocardium or vascular resistance, probably resulting in increasing atrial pressure and AF occurrence. Organ damage, such as dilated LA cavity and reduced creatinine clearance, was more frequent in the highest quartile of the normal TSH or hypothyroidism groups. Such remodeled and degenerated tissues and cardiac and renal dysfunction might be easily acceptable for atrial tachyarrhythmia recurrence after catheter ablation. Our population with relatively high TSH levels within the reference range showed a greater preponderance of elderly women, similar to that previously reported on a subclinical hypothyroidism population,¹³ suggesting that quartile 4 is pathologically close to subclinical hypothyroidism.

Important basic research was reported by Zhang et al.⁶ They performed an electrophysiological study using a rat model and demonstrated that hypothyroidism resulted in an increased AF susceptibility. In addition, they found that the hypothyroid rats showed a significantly longer atrial effective refractory period and increased LA interstitial fibrosis than euthyroid rats. Atrial fibrosis can lead to slow conduction and increased conduction heterogeneity, thus favoring reentry formation and increasing AF vulnerability.¹⁴ The development of atrial fibrosis is a hallmark of structural remodeling in AF and is considered a substrate for AF perpetuation. In fact, several studies have linked more extensive atrial interstitial fibrosis to lower effectiveness of AF catheter ablation.¹⁴ Thus, it may be reasonable to assume that the high incidence of arrhythmia recurrence observed in the highest TSH euthyroid quartile is at least partly attributable to increased atrial fibrosis. Although free thyroxine levels did not significantly differ between quartile 4 and quartile 1 to 3, changes in serum TSH levels are better than triiodothyronine and thyroxine levels to assess thyroid function because TSH levels sensitively reflect the negative feedback of thyroid status.⁴

Dysthyroidism might be iatrogenic as a result of prescribing amiodarone in some patients. Treatment with amiodarone was more frequent in the hypothyroidism and high-normal TSH groups compared with their corresponding groups. It may be possible that patients treated with amiodarone had a

tendency toward increased atrial tachyarrhythmia recurrence because of iatrogenic high TSH levels. One may argue that the amiodarone use can be a marker of increased resistance to the AF treatment. However, multivariate analysis did not identify amiodarone use as a significant variable related to the risk of the recurrence.

Mechanistic Overlap Theory Between Paroxysmal AF and Nonparoxysmal AF

Two philosophies in AF ablation are generally accepted: (1) elimination of triggers that mostly originate in the PVs and (2) alteration of AF substrates, such as LA lines and posterior wall isolation. Patients with paroxysmal AF generally have triggers from the PV only, whereas those with nonparoxysmal AF are more likely to have abnormalities of the atrial substrate in addition to triggers from PV.² Thus, clinical success can be better achieved in patients with paroxysmal AF than in those with nonparoxysmal AF. However, recent reports have highlighted the heterogeneity within patients with paroxysmal AF, indicating that a subgroup of paroxysmal AF has the same arrhythmia substrate as nonparoxysmal AF and is resistant to PVI as a result.^{15,16}

The ablation strategy taken in the present study was mostly limited to PVI. In other words, substrate modifications were done in a few patients. Thus, what made the difference in the long-term outcome between patients of TSH quartile 1 to 3 and quartile 4 may have been the extent of the arrhythmia substrate, which is closely related to atrial fibrosis.¹⁴ Among analyzed subjects, the lowest prevalence of long-term arrhythmia recurrence after the last session was observed in quartile 1 to 3 patients with paroxysmal AF. This may explain the causal association of relatively high TSH levels and extensive AF substrate because all triggering PVs should have been isolated after the last session and patients with paroxysmal AF in general have a smaller arrhythmia substrate than those with nonparoxysmal AF. On the other hand, atrial tachyarrhythmia-free survivals in quartile 4 patients with paroxysmal AF were nearly identical with those with nonparoxysmal AF, as measured after both the first and the last session, indicating that the effectiveness of catheter ablation did not differ between quartile 4 patients with and without paroxysmal AF (Figure 3). This finding gives a new insight into understanding the mechanistic overlap theory between patients with paroxysmal and nonparoxysmal AF.^{15,16}

Future Directions

Because these results suggest a relationship between high TSH levels and atrial tachyarrhythmia recurrence, we may well expect the possibility of recurrence in patients after catheter ablation in consideration of TSH levels. It is feasible that a

higher level of TSH can be ameliorated by exogenous thyroid hormones. However, it has not been elucidated whether patients with subclinical hypothyroidism should be treated with thyroid hormones because administration of exogenous thyroid hormones can easily produce iatrogenic subclinical hyperthyroidism with AF.¹⁷ Also, previous studies have provided no clear evidence that additional thyroid hormone therapy in subjects with milder forms of subclinical hypothyroidism could improve lipid status and other cardiovascular risk factors,¹⁸ as well as symptoms associated with hypothyroidism.¹⁹ Alternatively, because hypothyroidism enhances atrial fibrosis, leading to increased AF substrate,⁶ adjunctive ablation strategies, such as ablation targeting low-voltage areas,^{14,20} may improve the atrial tachyarrhythmia-free survival in this subset of the patients.

Study Limitations

There are some limitations to this study. First, given the relatively small size of the population, a larger study would allow us to identify the TSH levels worthy of appropriate caution. A cutoff level of TSH for differentiating atrial tachyarrhythmia recurrence after ablation was not available because of the small number of patients. Second, this study was a retrospective assessment, although the registration and systematic follow-up for catheter ablation in our hospital was the essential basis for study analysis. Third, the thyroid functions were evaluated once just before the catheter ablation procedure because the prognostic information should be of the greatest importance at this point. However, serial measurements may have provided more clinically relevant information to discuss the relationship between ablation outcome and thyroid status, such as the duration of hypothyroid or high-normal TSH state. Finally, although the causal effect of atrial fibrosis on AF recurrence is one hypothesis to explain the worse outcome seen in patients with hypothyroidism or high-normal TSH levels, the atrial fibrosis was not evaluated in the present study.

Conclusion

We studied whether TSH levels are related to 3-year outcomes of catheter ablation of AF. A high TSH level, even a high-normal level, is an independent predictor of long-term atrial tachyarrhythmia recurrence. Therefore, TSH levels should be noted in patients undergoing catheter ablation for AF, especially paroxysmal AF.

Disclosures

None.

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